Psychopharmacology of Antidepressants and Mood Stabilizers

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Objectives for the next 40 minutes or so …

By the end of the seminar, each student should:

- Understand the basic proposed therapeutic mechanisms of the different classes of antidepressants and mood stabilizers.
- Understand potential side effects of the different classes of antidepressants and mood stabilizers.
- Develop an understanding of the use of certain antidepressants and/or mood stabilizers in various clinical settings.

Great Resources

The American Psychiatric Association Treatment guidelines can be located on line at:

http://psych.org

Or directly at:

http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm

Or, the MS-3 Clerkship core seminar website at:

http://cim.usuhs.mil/ps03001/core_seminar_series_lectures.htm

A Lot of Players (Neurotransmitters) in the mix …

- Serotonin (5HT)
- Norepinephrine (NE)

Depression focus

- Dopamine (DA)
- Glutamate

Bipolar focus

- GABA
- Acetylcholine

“The Field, Part I”

Degraders/Eliminators

Monoamine Oxidase – degrades NE, 5HT, and DA

Catechol-O-methyltransferase (COMT) – degrades NE and DA

Reuptake mechanisms/ “pumps” – reuptakes NE, 5HT, and DA

“The Field, Part II”

Receptors

SEROTONIN RECEPTORS

5HT-1A *stimulation* = decrease in anxiety, depression, OCD, bulimic behaviors, panic symptoms

5HT-2 and 3 *stimulation* = most of the side effects, including sexual side effects.

GLUTAMATE RECEPTORS

Primarily excitatory

Many types: Ionotropic, NMDA, AMPA

ACETYLCHOLINE RECEPTORS

CNS contains mostly the muscarinic type

“The Field, Part II”

Receptors

ALPHA RECEPTORS

Alpha-1 Blockade: Dizziness, drowsiness, and decreased blood pressure; Alpha-2 blockade – more 5HT???

DOPAMINE RECEPTORS

D1 – D5 are the receptors discussed most; implicated in psychosis

GABA RECEPTORS

GABA-A receptor – ETOH, benzos potentiates here

Factors to Consider in Choosing a First-Line Antidepressant Medication

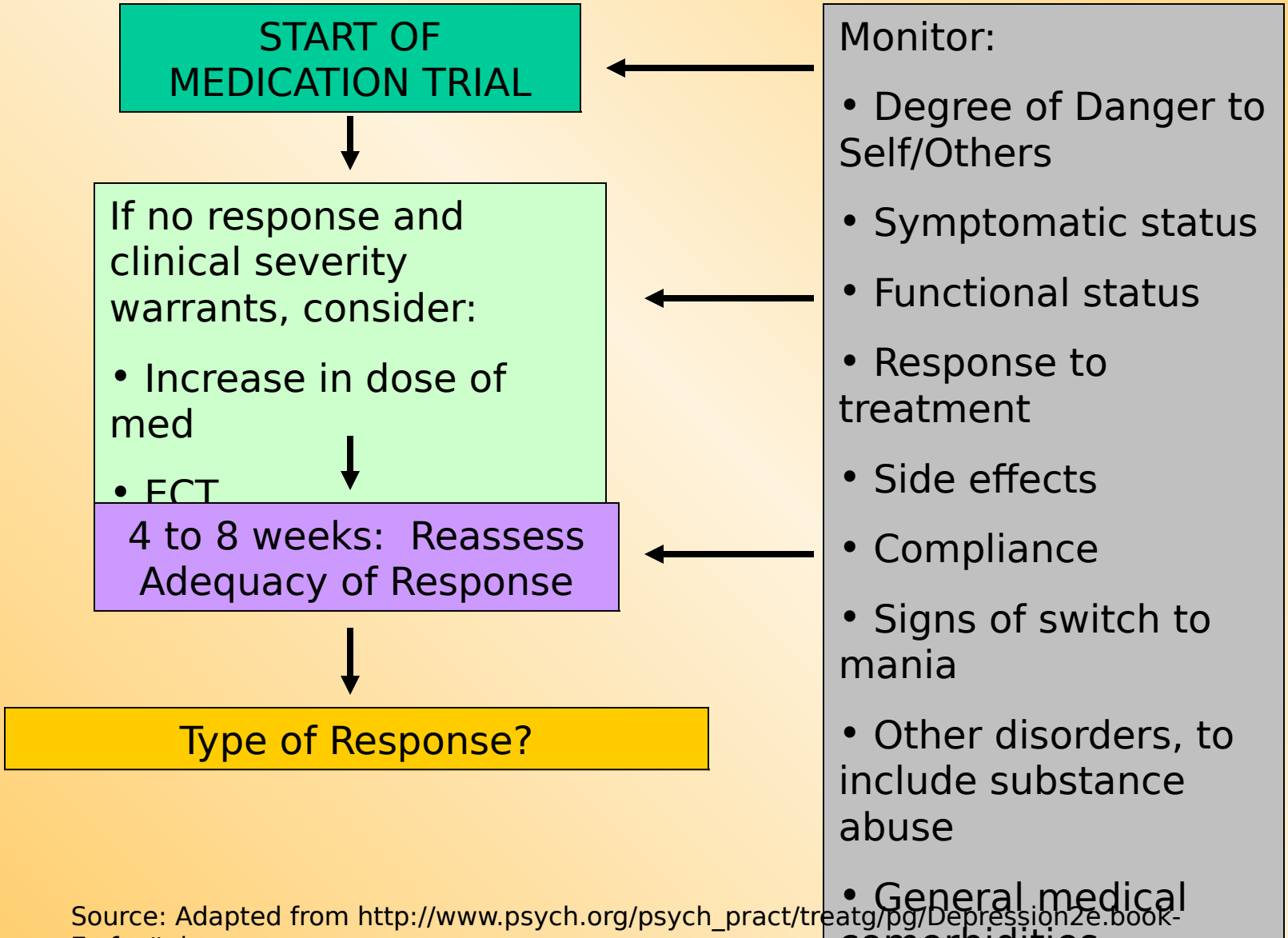
From the American Psychiatric Association Practice Guidelines

- Anticipated side effects and their safety or tolerability
- History of prior response in patient or family member
- Patient preference
- Cost
- Quantity or quality of clinical trial data
- MAOIs: Generally reserve for patient who do not respond to other treatments
- SSRIs or MAOIs: Consider for patients with atypical symptoms

Source: http://psych.org/psych_pract/treatg/pg/Depression2e.book-8.cfm?pf=y

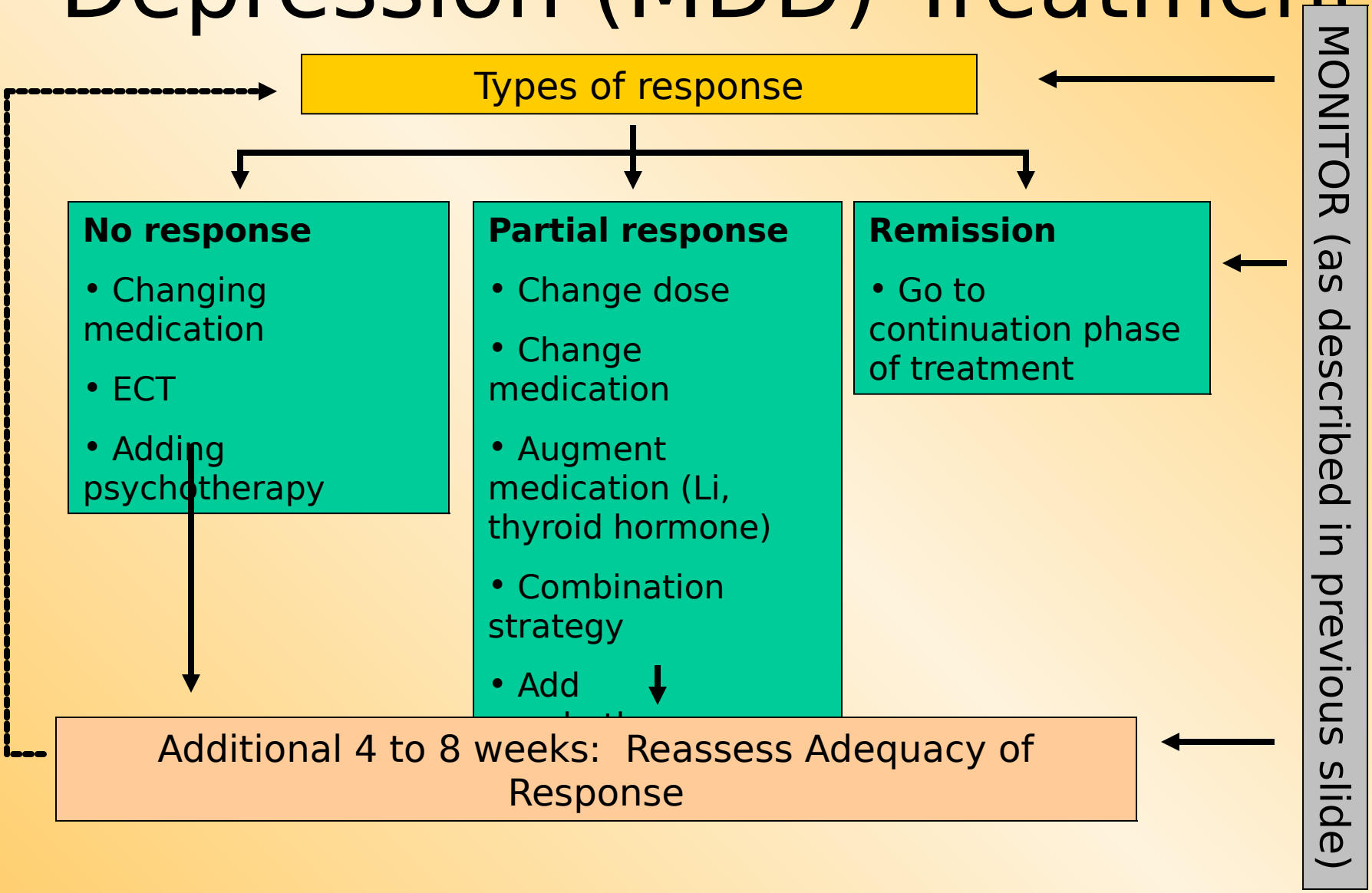
The Antidepressant Tour

Depression (MDD) Treatment


START OF MEDICATION TRIAL
If no response and clinical severity warrants, consider:
• Increase in dose of med
• ECT
4 to 8 weeks: Reassess Adequacy of Response
Type of Response?
Monitor:
• Degree of Danger to Self/Others
• Symptomatic status
• Functional status
• Response to treatment
• Side effects
• Compliance
• Signs of switch to mania
• Other disorders, to include substance abuse
• General medical

Source: Adapted from http://www.psych.org/psych_pract/treatg/pg/Depression2e.book-

Depression (MDD) Treatment



Source: Adapted from http://www.psych.org/psych_pract/treatg/pg/Depression2e.book-7.cfm#ai

Potentially Useful Info

FDA indications of commonly used psychiatric medications

****** Medications and FDA indications as of 13 April 2004**								
	MDD	**OCD**	**Panic d/o**	**PTSD**	**Bulimia Nervosa**	**Anorexia Nervosa**	**GAD**	**Social Phobia**
Fluoxetine	**Yes**	**Yes**	**Yes**	**-**	**Yes**	**-**	**-**	**-**
Paroxetine	**Yes**	**Yes**	**Yes**	**Yes**	**-**	**-**	**Yes**	**Yes**
Citalopram	**Yes**	**-**	**-**	**-**	**-**	**-**	**Yes***	**-**
Sertraline	**Yes**	**Yes**	**Yes**	**Yes**	**-**	**-**	**Yes**	**Yes**
Venlafaxine	**Yes**	**-**	**-**	**-**	**-**	**-**	**Yes**	**Yes**
Mirtazipine	**Yes**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Nefazadone	**Yes**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Burproprion	**Yes**	**-**	**-**	**-**	**-**	**-**	**-**	**-**

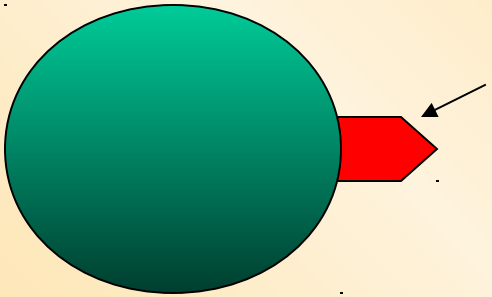
*Isomer of Citalopram (Escitalopram) has the indication for GAD

Potentially Useful Info

Dose ranges of commonly used antidepressant and antianxiety psychiatric medications

MEDICATION (generic)	DOSE RANGE (per day)
Fluoxetine (Prozac)	20-60mg
Paroxetine (Paxil)	20-60mg
Escitalopram (Lexapro)	10-30mg
Citalopram (Celexa)	20-60mg
Sertraline (Zoloft)	50-200mg
Venlafaxine (Effexor)	37.5-225mg
Mirtazipine (Remeron)	15-45mg
Nefazadone (Serzone)	150-300mg
Burproprion (Wellbutrin)	150mg-300mg

Antidepressants



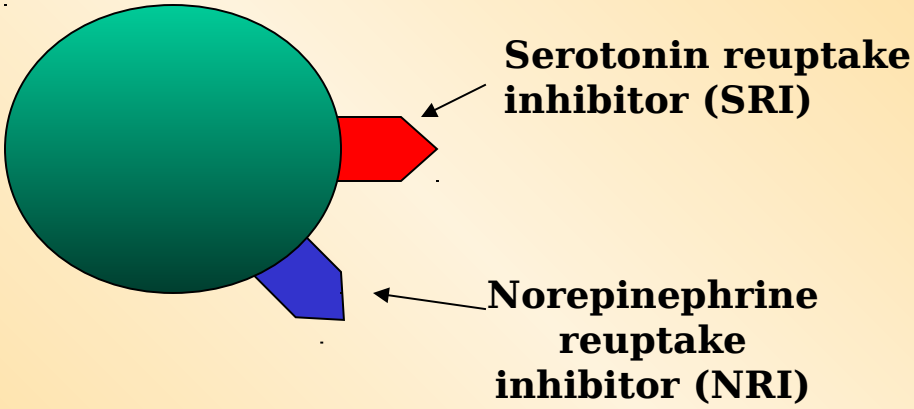
Sertraline (Zoloft); Fluoxetine (Prozac); Citalopram (Celexa); Escitalopram (Lexapro); Paroxetine (Paxil)

First-line for depression; some have FDA-indication for Anxiety Disorders.

What you should know:

- Probably all equally effective
- Half-lives different for each (Paxil shortest, Prozac longest)
- Some have many potential drug-drug interactions (e.g., Paxil, Prozac)
- Possess “secondary” components in addition to SRI

Antidepressants



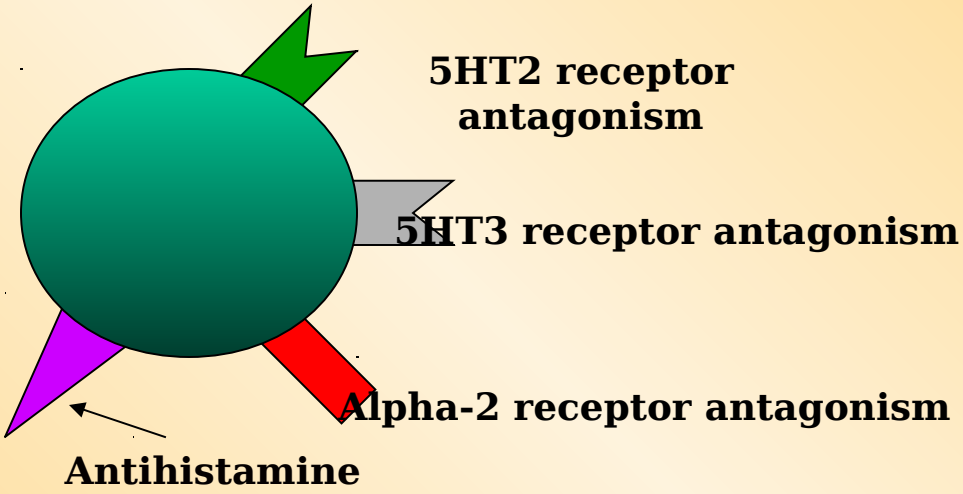
VENLAFAXINE (EFFEXOR)

Dual action medication for treatment of depression and anxiety. Performs more like an SSRI at doses below 150mg/day. Has an XR (Extended release formulation); more expensive.

What you should know:

- Possible increase in blood pressure (diastolic)
- Very few drug-drug interactions

Antidepressants



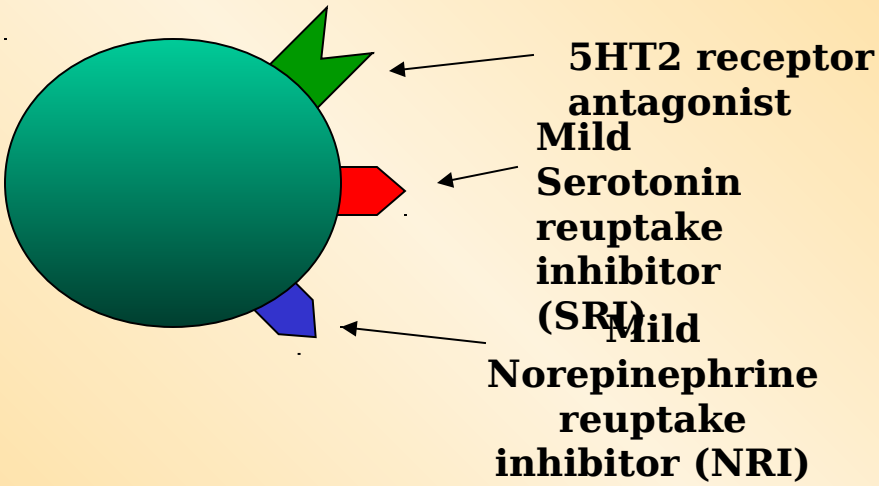
MIRTAZAPINE (REMERON)

Alpha-2 receptor antagonism works to release "brake" – in effect, increasing serotonin release. 5HT2 and 5HT3 receptor antagonist work to reduce side effects.

What you should know:

- Very few drug-drug interactions
- Side effects to patient's advantage – causes weight gain and helps with sleep

Antidepressants



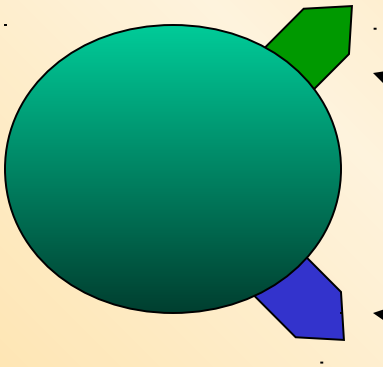
NEFAZADONE (SERZONE)

Medication used for depression and anxiety. It has mild SRI and NRI properties. Attempts to reduced side effects with 5HT2 receptor antagonism.

What you should know:

- Has SE of fatal hepatotoxicity
- One of the few antidepressants without sexual side effects
- Many potential drug-drug interactions

Antidepressants



Dopamine reuptake inhibitor (DRI)

Norepinephrine reuptake inhibitor (NRI)

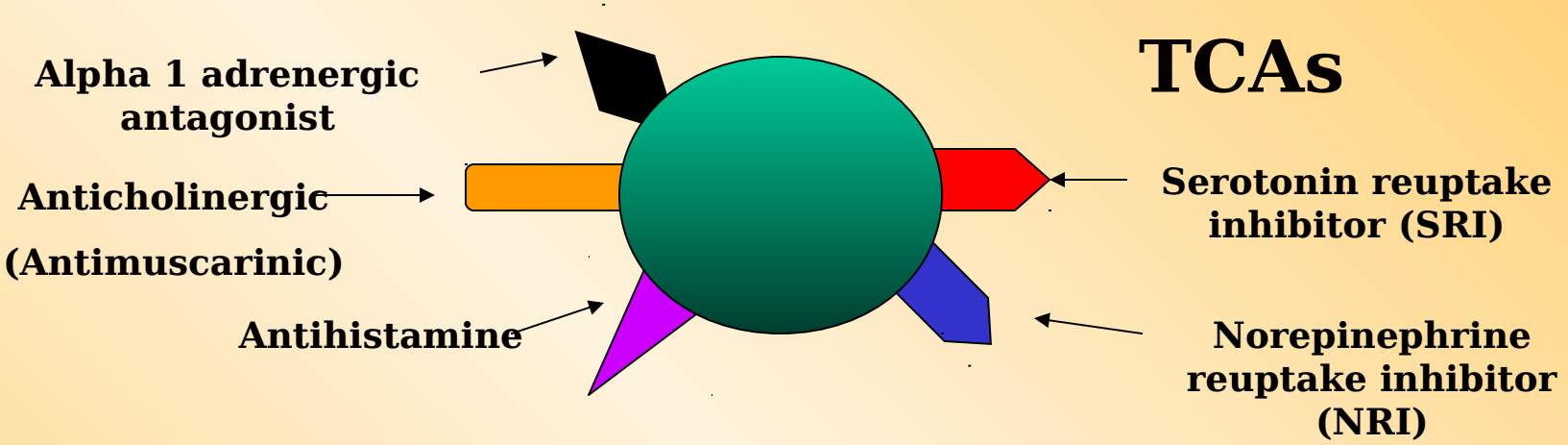
BUPROPRION (WELLBUTRIN)

Another dual action medication. Mainly treats depression. Has SR (sustained release formulation) and XL (extended release formulation). XL is the once a day formulation.

What you should know:

- Contraindicated in patients with seizures and eating disorders
- May be used to counteract sexual SE from SSRIs
- ADHD medication?

Antidepressants

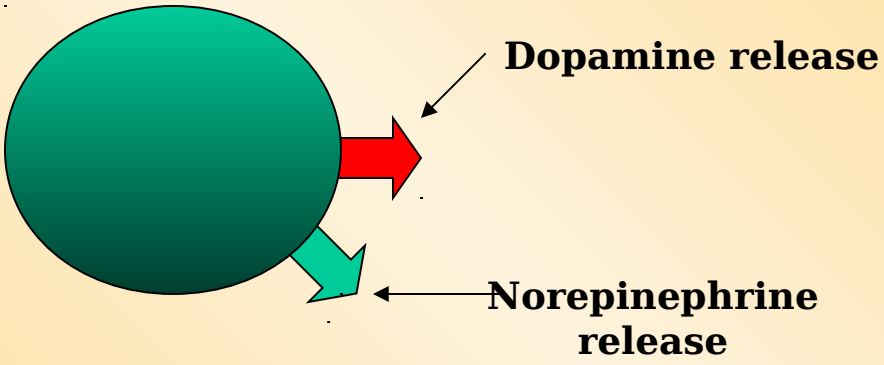


TCAs (Tricyclic antidepressants): Looks good? Maybe too much of a good thing; divided into tertiary vs. secondary TCAs. Secondary TCAs traditionally have less severe side effects.

What you should know:

- Lethal in overdose (1 week supply is enough)
- Treatment for chronic pain
- As effective a treatment as SSRIs
- Many potential drug-drug interactions

Antidepressants



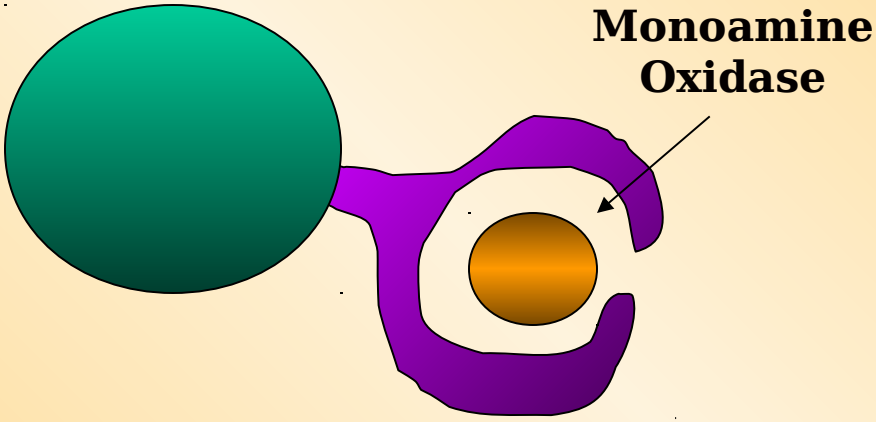
Methylphenidate

Acts to release the stores of dopamine and norepinephrine.

What you should know:

- Useful for apathetic depression in medically ill patients
- Used for ADHD; different release mechanisms available

Antidepressants



Monoamine Oxidase Inhibitors (MAOI)

What you should know:

- Used for atypical depression; used in refractory cases
- Dietary restrictions
- Switching “to” or “from” MAOI requires “wash out” period
- Some are irreversible; others are reversible

Mood Stabilizer Tour

LITHIUM

(Eskalith)

- Mildly proserotonergic; mechanism is thought to be at level of *G-proteins and other second messengers*

- *Excreted unchanged* by the kidney

- More effective in *pure mania and bipolar depression*

- Studies indicate *protective effect against suicide*

- *Side effects* are the rule rather than exception – large reason for noncompliance (e.g., nausea, tremor, sedation, weight gain, acne)

- Long term therapy may have kidney and thyroid effects

VALPROIC ACID

(Depakote)

-*Mechanism:* Unknown for certain, probably increases/enhances GABA action. Also blocks sodium/calcium channels function.

- Best used in *mixed and rapid cycling bipolar patients*.

- Side effects include *GI side effects, tremor, sedation, weight gain, alopecia*. Really bad things: *Hemorrhagic pancreatitis and aplastic anemia, fatal hepatotoxicity.*

- Teratogenic effects: *Neural tube defects*

- Loading doses for acute presentations is *20 mg/kg*

- *Baseline labs: CBC, LFTs, BhCG.*

CARBAMAZEPINE
(Tegretol)

- *Mechanism:* Unknown for certain; does interfere with sodium and potassium channels; (?)increases GABA function.

- Effective in acute mania.

- *Induces* its own metabolism; many *inductions/inhibitions* of other medications (ex. OCPs)

- *Side effects:* Neurological, GI, rash, hyponatremia. Really bad things: *Agranulocytosis, liver failure.*

- Teratogen: Neural tube defects.

- Labs: CBC, LFTs, Chem panel, BhCG.

LAMOTRIGINE
(Lamictal)

-*Mechanism:* Thought to inhibit sodium channels and inhibit release of glutamate.

- Most effective in bipolar depression.

- Side effects: Headache, blurred vision, nausea, rash. Really bad: *Stevens-Johnson syndrome*.

- Special attention when given with valproic acid (lamotrigine levels increase).

Other anticonvulsants (generally not first line): *Gabapentin (Neurontin) and Topiramate (Topamax)*

ATYPICAL ANTIPSYCHOTICS

- Atypicals are receiving indication for treatment of acute mania

- Examples: Olanzapine (Zyprexa); Risperidone (Risperdal). Probably more will follow

- Can be used alone or (more commonly) combined with a first line bipolar disorder agent.

BENZODIAZEPINES

- Don’t forget this tool!

- Very useful in the acute presentations of bipolar disorder; not as useful/studied for use as maintenance.

Rational Use/ “Pearls”on the Ward/Clinic

- **Family history of previous treatment? If effective, it may also be effective in your patient.**
- **Medication efficacy for depression – regardless of combination – probably about 60-70% effective.**
- **When taking a history, was the previous medication trials really a “failure” – in other words, was the dosage and duration adequate?**
- **What are the target symptoms? Depression, irritability, anxiety, insomnia, etc.?**
- **Labs/studies – pregnancy test, LFTs, Chem panels, EKG, etc.**
- **Be “up front” about the side effects, especially sexual side effects - may help with compliance.**
- **Keep scheduling simple (qD vs. QID) – will help compliance.**
- **Look for possible interactions with concurrent medications.**
- **Look for potential contraindications – eating disorder, seizure**

Clinical Questions
What Would You Do?

65 y/o woman with MDD. Her most prominent problems are “not being able to sleep or eat.” She has multiple medications for other medical conditions.

25 y/o active duty male Marine with MDD. He was recently married, reluctant to take medications.

30 y/o female with MDD. She has history of bulimia; this has not been a problem for the past 10 years.

Clinical Questions
What Would You Do?

23 y/o pregnant female in second trimester with recurrence of MDD. She is willing to take medication.

20 y/o male with manic symptoms. His lithium has been maximized with some results; however, he is still pretty “out there.”

18 y/o male presents in a mixed bipolar state. He is quite irritable and now is physically threatening staff. Show of force is not effective.

“End of the Show”

QUESTIONS?